L26 ANSWER 6 OF 11 MEDLINE

96171638 Document Number: 96171638. PubMed ID: 8574151. Distribution of linear antigenic epitopes on GP120 encoded in sibling clones of novel New York HIV-1 subtype B isolates. Riley J P; Pestano G A; Harewood K; Alfred L J; Guyden J; Boto W M. (Department of Biology and Chemistry, City College of the City University of New York, NY 10031, USA.) CELLULAR AND MOLECULAR BIOLOGY, (1995) 41 Suppl 1 S83-91. Journal code: 9216789. ISSN: 0145-5680. Pub. country: France. Language: English.

AB We have initiated studies to characterize the predominant subtypes of HIV-1 which account for infections in a defined cohort of intravenous (IV) drug addicts. A region of ENV encoding the C2 to the V5 regions was amplified from the leukocytes of two subjects currently enrolled in a methadone maintenance program at the Addiction Research and Treatment Corporation (ARTC), in Brooklyn, New York. This region of the viral genome encodes the principal neutralizing determinant (PND) located in the V3 loop, the immunogenic CD4-binding site, and six other linear antigenic epitopes in the envelope glycoprotein, gp120. Phylogenetic tree analysis of the nucleotide sequences showed that the sibling clones RT1.4, RT1.15, RT1.17, RT1.21 and RT3.6, RT3.10, RT3.11, RT3.12 and RT3.15 derived from the isolates, RT1 and RT3, respectively, cluster with "group B" viruses at 99% confidence level. Marked intra-patient and inter-patient sequence variation was apparent in the V3 loop. The divergence included the presence of a previously unreported hexapeptide GPWGTF at the cap of the loop in the clones from RT1. The North American consensus hexapeptide, GPGRAF , was identified in the cap of the loop from the clones of RT3. Four of the five sibling clones from RT3 were closely related whereas the other clone, RT3.15, displayed five amino acid mutations downstream of the V3 cap. To assess the effect of sequence variation on the distribution of linear antigenic epitopes, complementary computer software programs, were used to analyze the gp120 residues. Eight analogous antigenic epitopes were identified in the clones from both isolates despite the marked divergence in the primary sequences.(ABSTRACT TRUNCATED AT 250 WORDS)

L5 ANSWER 1 OF 1 USPATFULL
97:33728 Multiple branch peptide constructions for use against HIV.
Sabatier, Jean M., Chateauneuf de Rouge, France
Benjouad, Abdelaziz, Cachan, France
Yahi, Nouara, Marseille, France
Fenouillet, Emmanuel, La Valette du Var, France
Mabrouk, Kamel, Marseille, France
Gluckman, Jean-Claude, Paris, France
Van Rietschoten, Jurphaas, Aix en Provence, France
Rochat, Herve, Mimet, France
Armel S.A., Steinsel, Luxembourg (non-U.S. corporation)
US 5622933 19970422
APPLICATION: US 1994-260086 19940615 (8)
PRIORITY: GB 1993-18901 19930913
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention teaches multiple branch peptide constructions (MBPCs) formed from a core matrix to which is attached peptides derived from the V3 loop of the envelope glycoprotein of HIV-1, and including the amino acid sequence GPGR (SEQ ID NO: 5), preferably in the form GPGRAF, but which peptides preferably are free of the amino acid sequences IGPGR (SEQ ID NO: 1) or IXXGPGR (SEQ ID NO: 3), where X is an amino acid residue, and the use of such MBPCs as a therapy against HIV. The MBPCs prevent virus/cell infection and cell-to-cell virus transmission between CD4.sup.+ cells and HIV without hindering the immunogenic role of the CD4.sup.+ cells. Moreover, the MBPCs are effective in blockading both CD4 receptors on lymphocytes and macrophages and GalCer receptors on colon epithelial cells. These MBPCs are not immunogenic nor toxic at doses of their intended use (<[10.sup.-3 M]), thus allowing for them to be used therapeutically.

CLM What is claimed is:
1. A method of treating HIV infections comprising administering to a patient such amount of a multiple branch peptide construction as is sufficient to induce in the patient a blood concentration of the multiple branch peptide construction of up to 10.sup.-4 molar, the multiple branch peptide construction being non-immunogenic at the aforesaid blood concentration and comprising a core matrix to which are bonded from 2 to 16 peptides which consist of the amino acid sequence GPGR succeeded by from 2 to no more than 4 amino acid residues.

2. A method according to claim 1 wherein from 4 to 12 peptides are bonded to the core matrix of the multiple branch peptide construction.

3. A method according to claim 1 wherein the core matrix is comprised of lysine residues.

4. A method according to claim 1 wherein there are spacers between the core matrix and the peptides.

5. A method according to claim 1 wherein the peptides are peptide analogues.

6. A method according to claim 1 wherein the peptides include at least one D-amino acid residue.

7. A multiple branch peptide construction which at a blood concentration of up to 10.sup.-4 molar is non-immunogenic and which comprises a core

matrix to which are bonded 2 to 16 peptides which consist of the amino acid sequence GPGR succeeded by from 2 to no more than 4 amino acid residues.

8. A peptide construction according to claim 7 wherein from 4 to 16 peptides are bonded to the core matrix of the multiple branch peptide construction.

9. A peptide construction according to claim 7 wherein the core matrix is comprised of lysine residues.

10. A peptide construction according to claim 7 wherein there are spacers between the core matrix and the peptides.

11. A peptide construction according to claim 7 wherein the peptides are peptide analogues.

12. A peptide construction according to claim 7 wherein the peptides include at least one D-amino acid residue.

13. A multiple branch peptide construction comprising a core matrix to which are bonded 8 peptides consisting of the amino acid sequence GPGRAF.

14. A peptide construction according to claim 13 wherein the core matrix is composed of lysine residues.

15. A multiple branch peptide construction comprising a core matrix to which are bonded 16 peptides consisting of the amino acid sequence GPGRAF.

16. A peptide construction according to claim 15 wherein the core matrix is composed of lysine residues.

17. A method of treating HIV infections comprising administering to a patient a multiple branch peptide construction comprising a core matrix to which are bonded 8-16 peptides consisting of the amino acid sequence GPGRAF.

18. A method according to claim 17 wherein the multiple branch peptide construction is administered at a concentration of less than 10.sup.-4 M.

19. A method according to claim 17 wherein the core matrix is comprised of lysine residues.

20. A composition useful for inhibiting syncytia formation resulting from the fusion of (1) at least one of an envelope of HIV end a cell membrane of an HIV-infected cell to (2) a membrane of an non-HIV-infected cell which has at, least one of a CD4 receptor and a GalCer receptor, the composition containing a multiple-branch peptide construction which comprises a core matrix to which are bonded 2 to 16 peptides which consist of the amino acid sequence GPGR succeeded by from 2 to no more than 4 amino acid residues.

21. A composition according to claim 20, wherein said non-HIV -infected cell is at least one member selected from the group consisting of a peripheral blood lymphocyte, a primary macrophage, and a colon epithelial cell.

22. A composition according to claim 20, wherein there are 8-16 peptides

consisting of the amino acid sequence GPGRAF bonded to the core matrix.

23. A composition useful for inhibiting the fusion of (1) at least one of an envelope of HIV and a cell membrane of an HIV -infected call to (2) a membrane of an non-HIV-infected cell which has at least one of a CD4 receptor and a GelCer receptor, the composition being appropriate to induce in a patient a blood concentration of up to 10.sup.-4 molar of a multiple branch peptide construction which comprises a core matrix to which are bonded 2 to 16 peptides which consist of the amino acid sequence GPGR succeeded by from 2 to no more than 4 amino acid residues.

24. A composition according to claim 23, wherein there are 8-16 peptides consisting of the amino acid sequence GPGRAF bonded to the core matrix.

25. A method of inhibiting fusion of (1) at least one of an envelope of HIV and a cell membrane of an HIV-infected cell to (2) a membrane of an non-HIV-infected cell which has at least one of a CD4 receptor and a GelCer receptor, comprising administering to a patient such amount of a multiple branch peptide construction as is sufficient to induce in the patient a blood concentration of the multiple branch peptide construction of up to 10.sup.-4 molar, the multiple branch peptide construction being non-immunogenic at the aforesaid blood concentration and comprising a core matrix to which are bonded from 2 to 16 peptides which consist of the amino acid sequence GPGR succeeded by from 2 to no more than 4 amino acid residues.

26. A method according to claim 25, wherein there are 8-16 peptides consisting of the amino acid sequence GPGRAF bonded to the core matrix.

27. A method according to claim 25, wherein said non-HIV -infected cell is at least one member selected from the group consisting of a peripheral blood lymphocyte, a primary macrophage, and a colon epithelial cell.

L6 ANSWER 7 OF 23 USPATFULL
2001:51571 Multideterminant peptides that elicit helper T-lymphocyte, cytotoxic T lymphocyte and neutralizing antibody responses against HIV-1.
Berzofsky, Jay A., Bethesda, MD, United States
Ahlers, Jeffrey D., Kensington, MD, United States
Pendleton, C. David, Bethesda, MD, United States
Nara, Peter, Frederick, MD, United States
Shirai, Mutsunori, Kagawa, Japan
The United States of America as represented by the Department of Health and Human Services, Washington, DC, United States (U.S. government)
US 6214347 B1 20010410
APPLICATION: US 1995-455685 19950531 (8)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention is directed to peptides of the HIV-1 envelope protein presenting multiple immune determinants. The peptide elicits both humoral and cell-mediated immune responses in mice having a variety of MHC types. In other embodiments, the invention is directed to immunogens composed of the peptides and methods for immunization employing them.

CLM What is claimed is:

1. A polypeptide having an amino acid sequence selected from the group consisting of AVAEGTDRVIEVVQGAYRAIRHIPRRIRQGLER (SEQ. ID. NO. 26), DRVIEVVQGAYRAIRHIPRRIRQGLER (SEQ. ID. NO. 38), DRVIEVVQGAYRAIR (SEQ. ID. NO. 39), and AQGAYRAIRHIPRRIR (SEQ. ID. NO. 40).

L6 ANSWER 9 OF 23 USPATFULL
2000:145889 Peptide compositions for the treatment of HIV.
Rubinstein, Arye, Monsey-Wesley Hills, NY, United States
Bloom, Barry R., Hastings on Hudson, NY, United States
Devash, Yair, Princeton Junction, NJ, United States
Cryz, Stanley J., Berne, Switzerland
Albert Einstein College of Medicine of Yeshiva University, Bronx, NY, United States (U.S. corporation)
US 6139843 20001031
APPLICATION: US 1997-946525 19971007 (8)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides for peptide conjugate compositions, methods of using the peptide conjugate compositions, and pharmaceutical compositions comprising the peptide conjugate compositions. The peptide conjugate compositions comprise peptides with amino acid sequences similar to the gp120 principal neutralizing domain (PND) of HIV , gp41, and Nef (p27) of HIV and carriers which enhance immunogenicity. The peptide conjugate compositions of the present invention may comprise a multivalent cocktail of several different peptide conjugates. Also provided by present invention is a method for reducing the level of HIV titers in a mammal by administering to the mammal a peptide composition of the present invention in an amount effective to reduce the level of HIV titers. The peptide conjugate compositions of the present invention induce prolonged antibody response in serum, a high level of antibody in the mucosa, and the production of cytotoxic lymphocytes. The peptide conjugate compositions of the present invention also elicit neutralizing antibodies and decrease viral loads in a subject.

CLM What is claimed is:
1. A method for treating a mammal infected with HIV comprising administering to said mammal a peptide composition comprising peptides KRIHIGPGRAFYT (SEQ ID NO:1), RSIHIGPGRAFYA (SEQ ID NO:6), KSITKGPGRVIYA (SEQ ID NO:7), KGIAIGPGRTLYA (SEQ ID NO:8), and SRVTLGPGRVWYT (SEQ ID NO:9), wherein each peptide is coupled to a PPD carrier, and wherein the peptide composition is administered in an amount effective to reduce the level of HIV titers in said mammal.

2. The method of claim 1, wherein the composition is administered intradermally.

3. The method of claim 1, wherein a PPD carrier is conjugated to each peptide via gluteralderhyde.

L6 ANSWER 10 OF 23 USPATFULL
2000:91547 HIV envelope polypeptides and vaccine.
Berman, Phillip W., Portola Valley, CA, United States
Genentech, Inc., South San Francisco, CA, United States (U.S. corporation)
US 6090392 20000718
APPLICATION: US 1997-889841 19970708 (8)
PRIORITY: US 1996-676737P 19960708 (60)
DOCUMENT TYPE: Utility; Granted.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Oligonucleotide sequences encoding gp120 polypeptides from breakthrough isolates of vaccine trials using MN-rgp120 and the encoded gp120 polypeptides are provided. Use of the gp120 polypeptides from one or more of the isolates in a subunit vaccine, usually together with MN-rgp120, can provide protection against HIV strains that are sufficiently different from the vaccine strain (e.g.; MN-rgp120) that the vaccine does not confer protection against those strains. Antibodies induced by the polypeptides are also provided.

CLM What is claimed is:

1. An isolated polypeptide comprising an HIV gp 120 amino acid sequence selected from the group consisting of Sequence ID Nos: 2, 5, 8, 10, 12, 16, 19, 23, 25, 28, 31, 33, 36, and 39, and fragments thereof, wherein each of said fragments comprises at least the V2, V3, and C4 domains of gp120.

2. The polypeptide of claim 1 wherein the polypeptide additionally comprises a flag epitope sequence.

3. The polypeptide of claim 2 wherein the flag epitope sequence is the HSV gD-1 flag epitope sequence.

4. The polypeptide of claim 2 wherein the flag epitope sequence is fused to the HIV gp120 amino acid sequence.

5. The polypeptide of claim 1 wherein said HIV gp 120 amino acid sequence is a fragment lacking the gp120 signal sequence.

6. The polypeptide of claim 5 wherein the polypeptide additionally comprises a flag epitope sequence.

7. The polypeptide of claim 5 wherein the flag epitope sequence is the HSV gD-1 flag epitope sequence.

8. The polypeptide of claim 1 wherein the polypeptide comprises an amino acid sequence selected from the group consisting of Sequence ID Nos. 2 and 5 and fragments thereof, wherein each of said fragments comprises at least the V2, V3, and C4 domains of gp120.

9. The polypeptide of claim 1 wherein the polypeptide comprises an amino acid sequence selected from the group consisting of Sequence ID Nos. 8 and 10 and fragments thereof, wherein each of said fragments comprises at least the V2, V3, and C4 domains of gp120.

10. The polypeptide of claim 1 wherein the polypeptide comprises an amino acid sequence selected from the group consisting of Sequence ID Nos. 12 and 16 and fragments thereof, wherein each of said fragments comprises at least the V2, V3, and C4 domains of gp120.

11. The polypeptide of claim 1 wherein the polypeptide comprises an amino acid sequence selected from the group consisting of Sequence ID Nos. 19 and 23 and fragments thereof, wherein each of said fragments comprises at least the V2, V3, and C4 domains of gp120.

12. The polypeptide of claim 1 wherein the polypeptide comprises an amino acid sequence selected from the group consisting of Sequence ID Nos. 25 and 28 and fragments thereof, wherein each of said fragments comprises at least the V2, V3, and C4 domains of gp120.

13. The polypeptide of claim 1 wherein the polypeptide comprises an amino acid sequence selected from the group consisting of Sequence ID Nos. 31 and 33 and fragments thereof, wherein each of said fragments comprises at least the V2, V3, and C4 domains of gp120.

14. The polypeptide of claim 1 wherein the polypeptide comprises an amino acid sequence selected from the group consisting of Sequence ID Nos. 36 and 39 and fragments thereof, wherein each of said fragments comprises at least the V2, V3, and C4 domains of gp120.

15. An oligonucleotide of not more than five kilobases encoding an HIV gp120 polypeptide sequence comprising an amino acid sequence selected from the group consisting of Sequence ID Nos. 2, 5, 8, 10, 12, 16, 19, 23, 25, 28, 31, 33, 36, and 39, and fragments thereof, wherein each of said fragments encodes at least the V2, V3, and C4 domains of gp120.

16. The oligonucleotide of claim 15 wherein the oligonucleotide additionally encodes a flag epitope.

17. The oligonucleotide of claim 15 wherein the flag epitope is the HSV gD-1 flag epitope.

18. The oligonucleotide of claim 16 wherein the sequence encoding the flag epitope is fused to the sequence encoding the HIV gp120 amino acid sequence.

19. The oligonucleotide of claim 15 wherein said amino acid sequence is a fragment lacking the gp120 signal sequence.

20. The oligonucleotide of claim 19 wherein the nucleotide sequence encoding said fragment is joined to a nucleotide sequence encoding a heterologous signal sequence.

21. The oligonucleotide of claim 20 wherein said nucleotide sequences are joined via a nucleotide sequence encoding a flag epitope sequence.

22. The oligonucleotide of claim 20 wherein the signal sequence is the HSV gD1 signal sequence and the flag epitope sequence is the HSV gD-1 flag epitope sequence.

23. A vector comprising the oligonucleotide of claim 15.

24. A host cell comprising the vector of claim 23.

25. A method of producing a polypeptide comprising culturing the host cell of claim 24 and recovering the polypeptide.

26. An oligonucleotide of not more than 5 kilobases comprising a nucleotide sequence selected from the group consisting of Sequence ID Nos: 1, 4, 7, 9, 11, 15, 18, 22, 24, 27, 30, 32, 35, and 38, and fragments thereof, wherein each of said fragments encodes at least the V2, V3, and C4 domains of gp120.

27. The oligonucleotide of claim 26 wherein the oligonucleotide comprises a nucleotide sequence selected from the group consisting of Sequence ID Nos. 1 and 4 and fragments thereof, wherein each of said fragments encodes at least the V2, V3, and C4 domains of gp120.

28. The oligonucleotide of claim 26 wherein the oligonucleotide

comprises a nucleotide sequence selected from the group consisting of Sequence ID Nos. 7 and 9 and fragments thereof, wherein each of said fragments encodes at least the V2, V3, and C4 domains of gp120.

29. The oligonucleotide of claim 26 wherein the oligonucleotide comprises a nucleotide sequence selected from the group consisting of Sequence ID Nos. 11 and 15 and fragments thereof, wherein each of said fragments encodes at least the V2, V3, and C4 domains of gp120.

30. The oligonucleotide of claim 26 wherein the oligonucleotide comprises a nucleotide sequence selected from the group consisting of Sequence ID Nos. 18 and 22 and fragments thereof, wherein each of said fragments encodes at least the V2, V3, and C4 domains of gp120.

31. The oligonucleotide of claim 26 wherein the oligonucleotide comprises a nucleotide sequence selected from the group consisting of Sequence ID Nos. 24 and 27 and fragments thereof, wherein each of said fragments encodes at least the V2, V3, and C4 domains of gp120.

32. The oligonucleotide of claim 26 wherein the oligonucleotide comprises a nucleotide sequence selected from the group consisting of Sequence ID Nos. 30 and 32 and fragments thereof, wherein each of said fragments encodes at least the V2, V3, and C4 domains of gp120.

33. The oligonucleotide of claim 26 wherein the oligonucleotide comprises a nucleotide sequence selected from the group consisting of Sequence ID Nos. 35 and 38 and fragments thereof, wherein each of said fragments encodes at least the V2, V3, and C4 domains of gp120.

L6 ANSWER 12 OF 23 USPATFULL
1999:155203 Synthetic vaccine for protection against human immunodeficiency virus infection.
Haynes, Barton F., Durham, NC, United States
Palker, Thomas J., Durham, NC, United States
Duke University, Durham, NC, United States (U.S. corporation)
US 5993819 19991130
APPLICATION: US 1995-546515 19951020 (8)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to immunogenic preparations of peptides comprising amino acid sequences corresponding to antigenic determinants of the envelope glycoprotein of HIV, covalently coupled, directly or through a spacer molecule, to carrier molecules suitable for vaccination of mammals.

CLM What is claimed is:
1. A peptide of the general formula Th-SP10(X) wherein: Th represents an amino acid sequence comprising a T helper epitope; SP10 represents a peptide consisting essentially of an amino acid sequence of up to about 35 units in length and corresponding to at least one antigenic determinant of the envelope glycoprotein of HIV recognized by B lymphocytes, said peptide being capable, when covalently linked to a carrier molecule, of inducing in a mammal the production of high titers

of type-specific antibodies against HIV; and (X) represents an amino acid sequence corresponding to a HIV protein sequence recognized by MHC Class I or Class II restricted cytotoxic T cells.

2. A peptide of the general formula: Th-SP10 wherein: Th represents an amino acid sequence comprising a T helper epitope; and SP10 represents a peptide consisting essentially of an amino acid sequence of up to about 35 units in length and corresponding to at least one antigenic determinant of the envelope glycoprotein of HIV recognized by B lymphocytes, said peptide being capable, when covalently linked to a carrier molecule, of inducing in a mammal the production of high titers of type-specific antibodies against HIV.

L6 ANSWER 21 OF 23 USPATFULL
1998:9182 Method to induce cytotoxic T Lymphocytes specific for a broad array of HIV-1 isolates using hybrid synthetic peptides.
Berzofsky, Jay A., Bethesda, MD, United States
Takahashi, Hidemi, Tokyo, Japan
Germain, Ronald N., Potomac, MD, United States
The United States of America as represented by the Department of Health and Human Services, Wahington, DC, United States (U.S. government)
US 5711947 19980127
APPLICATION: US 1993-95332 19930723 (8)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The instant invention describes the synthesis of short peptides, corresponding to the amino acid residues of the V3 loop of the gp160 envelope glycoprotein of HIV-1 numbered 315 to 329 by Ratner (Ratner, L. et al., Nature 313, 277 (1985)) in the strain IIIB, wherein the residue corresponding to number 325 in HIV-1 IIIB is substituted by the homologous residue from another clinical isolate or strain. The invention further describes the use of said peptides in pharmaceutical compositions and an immunization protocol which elicits cytotoxic T cells reactive to a broad range of isolates of HIV-1.

CLM What is claimed is:
1. A method of inducing cytotoxic T lymphocyte activity in a subject comprising a first administration with a recombinant viral vector expressing HIV envelope glycoprotein and an at least second administration with at least one chimeric synthetic polypeptide.

2. The method according to claim 1 wherein the synthetic chimeric polypeptide consists of amino acids from a first isolate of HIV corresponding to residues 315 to 329 of the gp160 envelope glycoprotein of HIV-1 lllB with a substitution of the amino acid corresponding to position 325 of HIV-1 IIIB isolate with an amino acid found at that position from a second HIV-1 isolate.

3. The method according to claim 1, wherein the recombinant virus is at least one selected from the group consisting of vSC25, vMN and vRF.

4. The method according to claim 1, wherein the first isolate is HIV-1 MN.

5. The method according to claim 1 wherein the chimeric synthetic polypeptide is selected from the group consisting of sequence I.D. numbers 16-26.

6. The method according to claim 1 wherein at least one of the chimeric polypeptides has the sequence RIHIGPGRAFXTTKN wherein X is an amino acid selected from the group consisting of valine, leucine and isoleucine and said at least second administration is effective to obtain a cytotoxic T lymphocyte response against a plurality of strains of HIV-1.

L10 ANSWER 6 OF 9 USPATFULL
1998:112053 Synthetic, three-dimensionally stabilized polypeptide mimics of HIV.
Satterthwait, Jr., Arnold C., Del Mar, CA, United States
Arrhenius, Thomas, San Diego, CA, United States
Chiang, Lin-Chang, San Diego, CA, United States
Cabezas, Edelmira, Bogota, Colombia
The Scripps Research Institute, La Jolla, CA, United States (U.S. corporation)
US **5807979** 19980915
APPLICATION: US 1995-456424 19950601 (8)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods for synthesizing three-dimensional stabilized peptides which mimic the three-dimensional configuration of the active site of a natural, biologically active protein are carried out by (1) noting the three-dimensional configuration of the active site of a known biologically active protein (2) noting the amino acid sequence and the hydrogen bonds existing between amino acids which hydrogen bonds are capable of maintaining the three-dimensional configuration of the active site and (3) producing a synthetic three-dimensional peptide to mimic the structure of the active site. The synthetic peptide is synthesized so as to have the same or a similar amino acid sequence to the amino acid sequence of the active site of the biologically active polypeptide but with the stabilizing hydrogen bonds being replaced by a bridging divalent radical selected from the group of --(N)--C(CH.sub.3).dbd.N(H.sup.+)--CH.sub.2 --(N)--; --(N)--C(CH.sub.3).dbd.N(H.sup.+)--CH.sub.2 --CH.sub.2 --(N)--; and --(N)--N.dbd.CH--CH.sub.2 --CH.sub.2 --CH.sub.2 --(C)--. The stabilized three-dimensional peptide obtained is then isolated from the reaction mixture. The invention makes it possible to produce a wide range of biologically active compounds which have stable three-dimensional structures which allow the compounds to be used to obtain, for example, stabilized three-dimensional peptides which mimic the antigenic sites on viral envelopes which are useful as vaccines.

CLM What is claimed is:
1. A compound which mimics the V3 loop of gp 120 of HIV having binding activity with respect to anti-HIV antibodies, the compound being represented by the following structure (SEQ ID NO: 141): ##STR42## wherein I represents isoleucine, G represents glycine, P represents proline, R represents arginine and A represents alanine.

2. A compound which mimics the V3 loop of gp 120 of HIV having binding activity with respect to anti-HIV antibodies, the compound being represented by the following structure (SEQ ID NO: 142): ##STR43## wherein S represents serine, I represents isoleucine, G represents glycine, P represents proline, R represents arginine, A represents alanine, and F represents phenylalanine.

3. A compound which mimics the V3 loop of gp 120 of HIV having binding activity with respect to anti-HIV antibodies, the compound being represented by the following structure

(SEQ ID NO: 143): ##STR44## wherein S represents serine, I represents isoleucine, G represents glycine, P represents proline, R represents arginine, A represents alanine, F represents phenylalanine and Y represents tyrosine.

4. A compound which mimics the V3 loop of gp 120 of HIV having binding activity with respect to anti-HIV antibodies, the compound being represented by the following structure (SEQ ID NO: 144): ##STR45## wherein S represents serine, I represents isoleucine, G represents glycine, P represents proline, R represents arginine, A represents alanine, F represents phenylalanine, Y represents tyrosine and T represents threonine.

5. A compound which mimics the V3 loop of gp 120 of HIV having binding activity with respect to anti-HIV antibodies, the compound being represented by the following structure (SEO ID: 134): ##STR46## wherein A represents alanine, R represents arginine, Q represents glutamine, H represents histidine, C represents cysteine, (Acm) represents acetylated methionine, N represents asparagine, I represents isoleucine, S represents serine and K represents lysine.

L18 ANSWER 2 OF 6 USPATFULL
2003:26241 HIV-1 group O antigens and uses thereof.
DeLaporte, Eric, Saint Jean de Cuculles, FRANCE
Peeters, Martine, Saint Jean de Cuculles, FRANCE
Saman, Eric, Bornem, BELGIUM
Vanden Haesevelde, Marleen, Oudenaarde, BELGIUM
Innogenetics, N.V., BELGIUM (non-U.S. corporation)
US 6511801 B1 20030128
WO 9904011 19990128
APPLICATION: US 2000-462917 20000403 (9)
WO 1998-EP4522 19980720
PRIORITY: EP 1997-870110 19970718
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The claimed invention relates to an HIV-1 group O envelope antigen comprising SEQ ID NO: 100, and the use of said antigen as a reagent in the diagnosis of HIV-1 group O infection, and a kit therefore.

CLM What is claimed is:
1. An isolated antigen from the HIV-1 group O strain gp160 env precursor protein comprising the amino acid sequence of SEQ ID NO:100.

2. A method for detecting anti-HIV-1 antibodies in a sample comprising: a) contacting the sample with an isolated antigen from the HIV-1 group O strain gp160 env precursor protein comprising the amino acid sequence of SEQ ID NO:100, b) allowing the isolated antigen and anti-HIV antibodies to interact, and c) detecting the interaction between the antigen and the anti-HIV antibodies.

3. A kit for detecting HIV-1 antibodies comprising an isolated antigen from the HIV-1 group O strain gp160 env precursor protein comprising the amino acid sequence of SEQ ID NO:100.

4. An immunogenic composition comprising: a) an isolated antigen from the HIV-1 group O strain gp160 env precursor protein which

comprises the amino acid sequence of SEQ ID NO:100; and b) a pharmaceutically acceptable carrier.

L18 ANSWER 3 OF 6 USPATFULL
2000:105423 Selectively deglycosylated human immunodeficiency virus type 1 envelope vaccines.
Essex, Myron E., Sharon, MA, United States
Lee, Tun-Hou, Newton, MA, United States
Lee, Woan-Ruoh, Brookline, MA, United States
Lee, Chun-Nan, Brookline, MA, United States
President and Fellows of Harvard College, Cambridge, MA, United States (U.S. corporation)
US 6103238 20000815
APPLICATION: US 1992-850770 19920313 (7)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Selective deglycosylation of HIV-1 envelope proteins enhances their ability to elicit a protective immune response in people. Glycosylation can reduce or prevent immunological recognition of envelope protein domains. Selective deglycosylation exposes these domains and improves the opportunity for a protective immune response. Deglycosylation which produces substantial conformational changes (as determined by loss of infectivity) should be avoided. Recombinant HIV-1 envelope glycoproteins are generated which have primary amino acid sequence mutation(s) in consensus sequence(s) for N-linked glycosylation (sugar attachment), so as to prevent glycosylation at that site(s). The position of such genetic deglycosylation is important and should be between the C terminus of gp120 and the Cys at the N-terminal side of the cysteine loop containing the hyper-variable region 3 (V3) (this Cys is generally positioned about at residue 296, counting from the N-terminus of gp120). The mutant glycoprotein should be deglycosylated such that the total molecular mass of the mutant gp120 component is less than 90% (more preferably less than 75%) of the corresponding fully glycosylated wild type gp120 component to maximize a useful immune response.

CLM What is claimed is:
1. A composition comprising a mutant recombinant human immunodeficiency virus type 1 (HIV-1) envelope glycoprotein which is mutated in its primary amino acid sequence with respect to a wild type HIV-1 envelope glycoprotein, said mutant glycoprotein including two or more N-linked carbohydrate consensus amino acid sequence mutations so as to effect partial deglycosylation, said mutation being positioned between the C terminus of gp120 and the Cys at the N-terminal side of the gp120 cysteine loop containing the third hypervariable sequence (V3), said Cys being approximately at amino acid position 296, said mutant glycoprotein being sufficiently deglycosylated such that the total molecular mass of the mutant gp120 component is less than 75% of the corresponding fully glycosylated wild type gp120 component, said mutant glycoprotein being effective, when present as a component of a complete HIV virion, to enable viral infectivity.

2. The mutant glycoprotein composition of claim 1, wherein said virus is human immunodeficiency virus type 1, strain selected from the group consisting of MN, HXB2, IIIB, LAI, NL43, MFA, BRVA, SC, JH3, ALAI, BALI, JRCSF, OYI, SF2, NY5CG, SF162, JFL, CDC4, SF33, AN, ADA, WMJ2, RF, ELI, Z2Z6, NDK, JY1, MAL, U455, and Z321.

3. The mutant glycoprotein composition of claim 1, wherein said glycoprotein is gp160.

4. The mutant glycoprotein composition of claim 1, wherein said glycoprotein is gp120.

5. The mutant glycoprotein composition of claim 1, wherein said primary amino acid sequence is mutated such that one or more consensus N-linked glycosylation sequence mutation is a substitution of Asn, Ser, or Thr with a different amino acid.

6. The mutant glycoprotein composition of claim 1 wherein there are deglycosylations at multiple N-linked glycosylation attachment sites in the region between the C terminus of gp120 and the Cys on the N-terminal side of the cysteine loop containing hypervariable region 4 (V4).

7. The mutant glycoprotein composition of claim 1 in which at least one of the N-linked glycosylation sequences corresponding to positions 289 and 356 are not mutated.

8. The mutant glycoprotein of claim 1 in which at least one of the N-linked glycosylation sequences corresponding to the following position is deglycosylated: 386, 392, 397, 406 and 463.

9. A method of producing antibodies comprising: (a) administering to a mammal a mutant envelope protein, said protein being mutated in its primary amino acid sequence with respect to a wild type HIV-1 envelope glycoprotein, said mutant glycoprotein including two or more N-linked carbohydrate consensus amino acid sequence mutations so as to effect partial deglycosylation, said mutations being positioned between the C terminus of gp120 and the Cys at the N-terminal side of the gp120 cysteine loop containing the third hypervariable sequence (V3), said Cys being approximately at amino acid position 296, said mutant glycoprotein being sufficiently deglycosylated such that the total molecular mass of the mutant gp120 component is less than 75% of the corresponding fully glycosylated wild type gp120 component, said mutant glycoprotein being effective, when present as a component of a complete HIV virion, to enable viral infectivity; and (b) recovering said antibodies.

10. The antibodies of claim 9 wherein said antibodies are monoclonal antibodies.

L18 ANSWER 5 OF 6 USPATFULL
1998:65353 HIV-specific synthetic antigens and their use.
Conley, Anthony J., Exton, PA, United States
Arnold, Beth A., Quakertown, PA, United States
Boots, Lynn J., Lansdale, PA, United States
Keller, Paul M., Lansdale, PA, United States
Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)
US 5763574 19980609
APPLICATION: US 1996-625691 19960404 (8)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Immunological conjugates of HIV-specific selected principal neutralization epitopes are prepared. These epitopes bind 19b, a broadly neutralizing human monoclonal antibody specific for the HIV gp120. The epitopes are identified from oligopeptide epitope libraries. The conjugates are useful for vaccination against AIDS or ARC, as well

as in the production of other HIV-specific broadly neutralizing antibodies for passive immunity against AIDS or ARC.

CLM What is claimed is:

1. An antigenic conjugate of HIV-specific, selected principal neutralization epitopes covalently linked to purified outer membrane proteosome of Neisseria meningitidis, wherein said conjugate is of the formula (SPNE).sub.n .about.(OMPC) wherein: SPNE is the Selected Principal Neutralization Epitope of HIV, which is a polypeptide of one or more amino acid sequences selected from the group consisting of amino acid sequences of SEQ.ID.NO.:1-17 and 33; OMPC is purified outer membrane proteosome complex of Neisseria meningitidis, n is the number of polypeptides of SPNE covalently linked to OMPC and is 1-200; .about.indicates covalent linkage.

2. The antigenic conjugate of claim 1 wherein the covalent linkage between SPNE and OMPC consists essentially of a bigeneric spacer.

3. An HIV-specific selected principal neutralization epitope polypeptide having any of the sequences selected from the group consisting of SEQ.ID.NO.:1-17 and 33.

4. An HIV-specific selected principal neutralization consensus polypeptide having any of the consensus sequences, said consensus sequences selected from the group consisting of amino acid sequences of SEQ.ID.NO.:5, 9, and 17.

5. The antigenic conjugate of claim 1 wherein said conjugate is substituted with A.sup.-, which is an anion or polyanion at physiological pH, said A.sup.- consisting of one to five residues of anions selected from the group consisting of carboxylic, sulfonic, propionic, or phosphonic acid; or a pharmaceutically acceptable salt thereof.

L14 ANSWER 1 OF 3 WPIDS (C) 2003 THOMSON DERWENT
AN 2002-028342 [04] WPIDS
DNC C2002-008069
TI Vaccine that induces humoral, cellular and mucosal immunity against HIV-1 comprises modified recombinant envelope protein.
DC A96 B04 D16
IN LAVALLEE, C; THIBODEAU, L
PA (MOND-N) FOND MONDIALE RECH & PREVENTION SIDA
CYC 1
PI FR 2806912 A1 20011005 (200204)* 23p
ADT FR 2806912 A1 FR 2000-4310 20000404
PRAI FR 2000-4310 20000404

AB FR 2806912 A UPAB: 20020117
NOVELTY - The use of a recombinant Env protein from HIV-1 in which the V3 loop is partially or completely deleted, in order to prepare a vaccine that induces humoral, cellular and mucosal immunity against HIV-1, and vaccinal compositions comprises this protein.
ACTIVITY - Anti-HIV.
No biological data given.
MECHANISM OF ACTION - None given.
USE - Prevention of HIV and AIDS.
Dwg.0/0

L14 ANSWER 3 OF 3 WPIDS (C) 2003 THOMSON DERWENT
AN 1982-22283E [12] WPIDS
TI Immunosome(s) consisting of viral antigen attached to liposome(s) - useful in vaccines having no side effects.
DC B04 D16
IN BOUDREAULT, A; NAUD, P; THIBODEAU, L
PA (FRAP-N) FRAPPIER ARMAND INST
CYC 13
PI EP 47480 A 19820317 (198212)* EN 12p
R: AT BE CH DE FR GB IT LI LU NL SE
JP 57118794 A 19820723 (198235)
EP 47480 B 19860205 (198606) EN
R: BE DE FR GB
DE 3173713 G 19860320 (198613)
JP 06076340 B2 19940928 (199437) 6p
ADT EP 47480 A EP 1981-106848 19810902; JP 06076340 B2 JP 1981-139627 19810904
FDT JP 06076340 B2 Based on JP 57118794
PRAI US 1980-184264 19800905

AB EP 47480 A UPAB: 19930915
Prodn. of immunosomes comprises treating pre-formed liposomes so as to make them receptive to antigen subunits (which then project out from the liposome surface), and then mixing with an antigenic viral subunit-detergent complex (A). The liposomes are made by solubilising phospholipid in the presence of a detergent, injecting the resulting soln. into a buffer, and finally dialysing.
Pref. a mixt. of phosphatidyl choline, cholesterol and lysolecithin (mole ratio 8:1:0.5) is solubilised in Tris-HCl buffer contg. about 30mM beta-D-octylglucoside (I), the soln. injected into phosphate-buffered saline, then dialysed. The immunosomes themselves are also claimed.
The immunosomes are useful in vaccines which are free of local or general secondary effects since they contain only the antigen and no impurities such as nucleic acids. They are more immunogenic than the viral subunits themselves; contain antigen units only on the outer surface and are prepd. without use of organic solvents or ultrasonic waves.

L17 ANSWER 2 OF 9 WPIDS (C) 2003 THOMSON DERWENT
AN 2001-122993 [13] WPIDS
DNN N2001-090325 DNC C2001-035684
TI New viral envelope proteins, useful for producing vaccines to treat human immunodeficiency virus-1 infections, comprises amino acid sequence mutations such that viral transmembrane-surface protein complex is more stable.
DC B04 D16 S03
IN BINLEY, J M; MADDON, P J; MOORE, J P; OLSON, W C; SCHUELKE, N
PA (AARO-N) AARON DIAMOND AIDS RES CENT; (PROG-N) PROGENICS PHARM INC
CYC 23
PI WO 2001000648 A1 20010104 (200113)* EN 109p
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: AU CA JP MX
AU 2000058842 A 20010131 (200124)
EP 1198468 A1 20020424 (200235) EN
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
JP 2003509013 W 20030311 (200319) 97p
ADT WO 2001000648 A1 WO 2000-US17267 20000623; AU 2000058842 A AU 2000-58842 20000623; EP 1198468 A1 EP 2000-944801 20000623, WO 2000-US17267 20000623; JP 2003509013 W WO 2000-US17267 20000623, JP 2001-507055 20000623
FDT AU 2000058842 A Based on WO 200100648; EP 1198468 A1 Based on WO 200100648; JP 2003509013 W Based on WO 200100648
PRAI US 1999-340992 19990625

AB WO 200100648 A UPAB: 20010307
NOVELTY - A viral envelope protein (I) comprising a viral surface protein (Ia) and a corresponding viral transmembrane protein (Ib), in which the viral envelope protein contains one or more amino acid sequence mutations that enhance the stability of the complex formed between (Ia) and (Ib), is new. Optionally (Ia) and (Ib) are encoded by different nucleic acids.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) an isolated nucleic acid (II) which comprises a nucleotide segment with a sequence encoding a complex (C) containing (Ia) and (Ib), in which the complex contains one or more amino acid mutations that enhance the stability of the complex formed between (Ia) and (Ib);

(2) a replicable vector (III) comprising (II);

(3) a host cell (IV) containing (III);

(4) a prophylactic or therapeutic vaccine (V) comprising (II);

(5) a (C) which comprises (Ia) and (Ib) of (I), in which (I) or (C) contains one or more amino acid sequence mutations that enhance the stability of the complex formed between (Ia) and (Ib), where (Ia) and (Ib) are encoded by different nucleic acids;

(6) a mutant human immunodeficiency virus (HIV) envelope protein (VI) encoded by (II);

(7) a purified protein (I), (C) or (VI);

(8) a vaccine which comprises (I) or (C);

(9) an antibody (VII), antibody chain, fragment or its derivative isolated or identified using the viral envelope protein encoded by (I);

(10) an isolated antibody heavy chain or light chain of (VII) or its fragment or oligomer;

(11) one or more complementarity determining regions (CDR) of (VII);

(12) an isolated nucleic acid molecule (VIII) encoding (VII), in which the nucleic acid molecule is RNA, genomic DNA or cDNA;

(13) an agent (IX) capable of inhibiting the binding of (VII);

(14) an agent (X) capable of binding (I) encoded by the recombinant (II);

(15) determining (M1) whether a compound is capable of inhibiting a viral infection involves:

(a) contacting an appropriate concentration of the compound with (I)

under conditions permitting binding of the compound to the protein;

(b) contacting the resulting complex with a reporter molecule under conditions that permit binding of the reporter molecule to the (I) in the absence of the compound;

(c) measuring the amount of bound reporter molecule; and

(d) comparing the amount of bound reporter molecule with the amount determined in the absence of the compound, where a decrease in the amount indicates that the compound is capable of inhibiting infection by the virus; or

(e) contacting an appropriate concentration of the compound with the host cell viral receptor or its molecular mimic to permit binding of the compound or receptor mimic in the absence of the compound;

(f) contacting the resulting complex with (I) under conditions that permit binding of the envelope protein and receptor or receptor mimic in the absence of the compound;

(g) measuring the amount of binding of envelope protein to receptor or receptor mimic; and

(h) comparing the amount of binding with the amount determined in the absence of the compound, where a decrease in the amount indicates that the compound is capable of inhibiting infection by the virus;

(16) a compound (XI) determined to be capable of inhibiting viral infection by (M1);

(17) a pharmaceutical composition comprising (XI) to be capable of inhibiting viral infection and a carrier;

(18) an antibody (XII) which binds to (I) or (C) but which does not cross react with the individual monomeric (Ia) or (Ib); and

(19) a virus like particle (XIII) which comprises (C).

ACTIVITY - Anti-HIV. No supporting data is given.

MECHANISM OF ACTION - Gene therapy; vaccine.

USE - (V) comprising a recombinant subunit protein, a DNA plasmid, a replicating viral vector, a non-replicating viral vector or its combination is useful for treating a viral disease (preferably HIV-1 in a subject) which involves immunizing a virally infected subject with (V). It is also useful for reducing the likelihood of a subject being infected with a virus (preferably, HIV). The vaccine comprising (I) or (C) is useful for stimulating or enhancing the production of antibodies against (I) or (C). (VII) or (VIII) is useful for reducing the likelihood of a HIV-1 exposed subject from becoming infected with HIV-1. It is also useful for treating a HIV-1 infected subject. (XI) and pharmaceutical compositions comprising (XI) are useful for inhibiting HIV-1 viral infection (claimed). The vaccine comprising (I) is also useful for reducing the severity of the viral disease which involves administering the vaccine prior to exposure of the subject to virus.

DESCRIPTION OF DRAWING(S) - The figure shows the different forms of human immunodeficiency-1 glycoproteins.

Dwg.1/15

L17 ANSWER 4 OF 9 WPIDS (C) 2003 THOMSON DERWENT
AN 2000-656164 [63] WPIDS
DNC C2000-198581
TI Synthetic peptides useful for preventing and treating HIV infection in mammals, comprising a conformationally constrained portion and a portion with continuous stretch of amino acids of predicted secondary structure.
DC B04 D16
IN BERNSTEIN, D; CHOWDHURY, A; KOZHICH, A; MOTSENBOCKER, M
PA (BERN-I) BERNSTEIN D; (CHOW-I) CHOWDHURY A; (KOZH-I) KOZHICH A; (MOTS-I) MOTSENBOCKER M
CYC 92
PI WO 2000058438 A2 20001005 (200063)* EN 69p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL

OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ
EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK
LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI
SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2000037740 A 20001016 (200106)
ADT WO 2000058438 A2 WO 2000-US8232 20000329; AU 2000037740 A AU 2000-37740 20000329
FDT AU 2000037740 A Based on WO 200058438
PRAI US 1999-126938P 19990329

AB WO 200058438 A UPAB: 20011129
NOVELTY - A peptide (I) 16 to 75 amino acids long comprising a first conformationally constrained portion (P1) 5 to 13 amino acids long with a cross-linked group of a human immuno-deficiency virus (HIV) envelope protein that induces neutralizing antibodies, and a second portion (P2) comprising a continuous stretch of at least 5 amino acids having a predicted secondary structure, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a pharmaceutical composition comprising (I) useful for prophylactic or therapeutic treatment of a mammal at risk for or infected with HIV;

(2) preparation of (I);

(3) a peptide (II) having a modification of a sequence from an envelope protein of a virus that fuses with a host cell in a pH independent manner, where the modification comprises replacement of an enhancing group of the envelope protein with a neutralizing group from the same virus;

(4) designing a peptide to elicit the production of neutralizing antibodies targeted to a virus that fuses with a host cell in a pH-independent manner, comprising obtaining a sequence of an envelope protein of the virus and replacing an enhancing group of the envelope protein sequence with a neutralizing group from the same virus.

ACTIVITY - Anti-HIV.

MECHANISM OF ACTION - Vaccine.

No supporting data is given.

USE - (I) is useful as vaccine for prophylactic or therapeutic treatment of a mammal for human immuno-deficiency virus (HIV) infection (claimed).

ADVANTAGE - (I) is useful for vaccinating against viruses that fuse their host in a pH independent manner.

Dwg.0/0

L17 ANSWER 5 OF 9 WPIDS (C) 2003 THOMSON DERWENT
AN 1999-550490 [46] WPIDS
DNC C1999-160500
TI Fusion glycoprotein comprising active polypeptide and retroviral envelope protein useful in immunoassays and as immunogens, especially for anti-human immune deficiency vaccines.
DC B04 D16
IN KAYMAN, S; PINTER, A
PA (PUBL-N) PUBLIC HEALTH RES INST NEW YORK
CYC 1
PI US 5952474 A 19990914 (199946)* 48p
ADT US 5952474 A CIP of US 1992-938100 19920828, Div ex US 1993-110300 19930820, US 1997-886642 19970701
FDT US 5952474 A Div ex US 5643756
PRAI US 1993-110300 19930820; US 1992-938100 19920828; US 1997-886642 19970701

AB US 5952474 A UPAB: 19991110
NOVELTY - Fusion glycoprotein (I) containing the N-terminal globular domain of a retroviral envelope (env) surface protein linked to a glycopeptide is new.

DETAILED DESCRIPTION - (I) is expressed by a vector comprising a biologically active amino acid sequence (II) from a protein lacking a hydrophobic glycosylation signal (HGS) located about 7 residues N-terminal to a Cys-Trp-Leu-Cys sequence, (II) is operably linked to the C-terminus of a polypeptide sequence (III) from a retroviral env protein. (III) is an N-terminal fragment of env and includes all Cys residue from the N-terminal globular domain with a N-glycan attachment site with an HGS located within 7 residues N-terminal to a Cys-Trp-Leu-Cys sequence.

An INDEPENDENT CLAIM is also included for a retroviral particle containing a recombinant gene encoding (I).

ACTIVITY - Antiviral.

MECHANISM OF ACTION - Vaccine.

USE - (II) particularly includes an epitope and can then be used in immunoassys for diagnostic detection of antibodies, receptors or other binding partners, in affinity chromatography, or as immunogens, particularly in protective vaccines or for production of monoclonal antibodies. Most particularly (I) is used to raise neutralizing antibodies against human immune deficiency virus (HIV)-1. Vectors used to express (I) can be constructed in bacteria to generate stable cell lines and can be used to infect a wide variety of cells. (I)-expressing cell cultures can be made quickly (without use of a selection marker) and the level of expression in mammalian cells is high, allowing simple and quick analysis during vaccine development.

ADVANTAGE - (I), or viral particles containing them, can be produced efficiently in mammalian cells; and retain glycosylation- and conformation-dependent epitopes (even where these are complex and involve several disulfide bonds). Expression in a virus particle ensures efficient antigen presentation, and production and purification of these particles is simpler and cheaper than purification of proteins. Viruses that are harmless to humans may be used for particle production.
Dwg.0/15

L17 ANSWER 6 OF 9 WPIDS (C) 2003 THOMSON DERWENT
AN 1999-229137 [19] WPIDS
DNC C1999-067382
TI New gp120 V1/V2 fusion proteins.
DC B04 D16
IN PINTER, A
PA (PINT-I) PINTER A; (PUBL-N) PUBLIC HEALTH RES INST NEW YORK
CYC 22
PI WO 9912556 A1 19990318 (199919)* EN 63p
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: AU CA JP US
AU 9893071 A 19990329 (199932)
EP 1011707 A1 20000628 (200035) EN
R: DE FR GB IT NL SE
ADT WO 9912556 A1 WO 1998-US18679 19980908; AU 9893071 A AU 1998-93071 19980908; EP 1011707 A1 EP 1998-945936 19980908, WO 1998-US18679 19980908
FDT AU 9893071 A Based on WO 9912556; EP 1011707 A1 Based on WO 9912556
PRAI US 1997-58155P 19970908

AB WO 9912556 A UPAB: 19990518
NOVELTY - A novel protein (A) comprises a gp120 V1/V2 domain of an HIV-1 strain and not comprising the gp120 V3 domain of an HIV-1 strain, where the protein does not bind CD4, the gp120 V1/V2 domain of the protein displaying an epitope which is recognized by an antibody which neutralizes at least one HIV-1 primary isolate

with a ND90 of at most 100 mu g/ml.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) a protein comprising a gp120 V1/V2 domain related region that is at least 50% identical to VKLTPLCVTLNCIDLRNATNATSNSNTTNTTSSSGGLMMEQGEIKNCS FNITTSIRDKVQKEYALFYKLDIVPIDNPKNSTNYRLISCNTSVITQA (I) and not comprising the gp120 V3 domain of an HIV-1 strain, where the protein does not bind CD4, the gp120 V1/V2 domain related region displaying an epitope which is recognized by an antibody which neutralizes at least one HIV-1 primary isolate with a ND90 of at most 100 mu g/ml;

(2) a protein comprising a gp120 V1/V2 domain of an HIV-1 strain and not comprising a gp120 V3 domain of an HIV -1 strain, where the protein does not bind CD4, the protein, when used to immunize a rat, being capable of eliciting an antibody which neutralizes at least one clade B HIV-1 primary isolate with a ND90 of at most 100 mu g/ml;

(3) monoclonal antibody which binds the gp120 V1/V2 domain of HIV-1 strain Case-A2 and neutralizes at least one clade B HIV-1 primary isolate and at least one clade D HIV-1 primary isolate with a ND90 of at most 100 mu g/ml;

(4) a nucleic acid molecule (NAM) encoding the protein (A);

(5) an expression vector comprising a NAM as in (4);

(6) a host cell comprising the vector as in (5)

(7) a hybrid protein comprising a first part and a second part, the first part comprising the protein (A), the second part comprising an amino terminal carrier protein comprising all or a portion of Friend MuLV gp70;

(8) a protein comprising a first portion and a second portion, the first portion being a V1/V2 domain region homologous to PCVKLTPCV, the second portion being a V1/V2 domain region homologous to SCNTSVITQACP, the first and second portions being linked by at least one disulfide bond.

USE - The proteins can be used for stimulating the formation of antibodies capable of neutralizing infection by an HIV viral isolate in mammals (claimed). They can also be used for therapeutic treatment of subjects already infected with HIV. They can also be used in immunoassays for anti-HIV antibodies and for the production of anti-HIV antiserum.

Dwg.0/13

L17 ANSWER 7 OF 9 WPIDS (C) 2003 THOMSON DERWENT
AN 1998-531557 [45] WPIDS
DNC C1998-159424
TI Mutant under-glycosylated HIV-1 envelope glyco protein composition - useful in, e.g. vaccines to protect mammals, especially humans, against HIV-1 infection or to treat such infections.
DC B04 D16
IN DESROSIERS, R C; REITTER, J N
PA (HARD) HARVARD COLLEGE
CYC 21
PI WO 9841536 A1 19980924 (199845)* EN 63p
RW: AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: AU CA JP US
AU 9865358 A 19981012 (199907)
ADT WO 9841536 A1 WO 1998-US3374 19980313; AU 9865358 A AU 1998-65358 19980313
FDT AU 9865358 A Based on WO 9841536
PRAI US 1997-40790P 19970314

AB WO 9841536 A UPAB: 19981111
A novel composition comprises a recombinant human immunodeficiency virus type 1 (HIV-1) envelope glycoprotein with an amino acid sequence altered with respect to wild type

HIV-1 by including a mutated consensus amino acid recognition sequence for N-linked carbohydrate attachment. The mutated sequence is positioned on gp120 between its N-terminus and the Cysteine (at approximately position 296) at the N-terminal side of the gp120 cysteine hypervariable region 3 (V3) loop. The recombinant envelope glycoprotein is not glycosylated in mammalian host cells as a result of the mutated sequence ('undergycosylated'), but is effective, when present as a component of a complete HIV virion, to support viral infectivity. Also claimed are vaccines comprising the composition to protect humans against HIV-1 infection, and antibodies (optionally monoclonal) produced by challenging a mammal with the composition.

USE - The compositions are useful, optionally with suitable carriers, in vaccines (claimed) or pharmaceutical compositions to protect humans against HIV-1 infection or treat such infections. Such vaccines may especially comprise mutated gp120 as above contained in an infective HIV virion (claimed). The compositions can also be administered to mammals to induce a protective immune response to prevent/delay HIV-1 infection (claimed) or to produce antibodies (claimed). The altered HIV-1 envelope proteins of the compositions may alternatively be administered by introducing, and allowing expression of, encoding DNA (e.g. using expression vectors). HIV-1 gp120 is heavily glycosylated (having approximately 55 % of its molecular mass contributed by N-linked carbohydrates) and previous work has demonstrated that, whilst some N-linked sites can be eliminated without impairing native structure or ability of the virus to replicate, others (located in the region described above) are essential for the virus to replicate. By selectively removing N-linked glycans within this region, an underglycosylated envelope glycoprotein capable of enhanced antibody response but retaining infectivity can be produced.

Dwg.0/22

L17 ANSWER 8 OF 9 WPIDS (C) 2003 THOMSON DERWENT
AN 1995-237146 [31] WPIDS
DNC C1995-109016
TI AIDS vaccine used against e.g. HTLV-III-B - contains synthetic V3 region peptide of Gp120 of HIV envelope.
DC B04 D16
PA (OKUD-I) OKUDA K; (TERU) TERUMO CORP
CYC 1
PI JP 07145078 A 19950606 (199531)* 17p
ADT JP 07145078 A JP 1993-292257 19931122
PRAI JP 1993-292257 19931122

AB JP 07145078 A UPAB: 19950810

AIDS vaccine contains synthetic V3 region peptide of gp120 of HIV envelope. The V3 region peptide has a branched lysine oligomer bound to the core at the C-terminal with the region. The average mol. wt. is 40000-60000.

V3 region peptide of gp120, derived from strains including HTLV-III-B, HTLV-Thai-A and HTLV-B types, in HIV envelope is synthesised and cysteine residue is introduced at the C-terminal, followed by binding with an N-terminal of branched chain lysine oligomer to give the AIDS vaccine. The C-terminal may be bound with a peptide of T-cell antigen epitope derived from HIV surface protein.

USE/ADVANTAGE - AIDS vaccine is used against HTLV-III-B, HTLV-Thai-A and HTLV-B types. The AIDS vaccine effective against a wide range of HIV is simply prepd.

In an example, antigen specific interleukin-2 (IL-2) productivity was determined in vaccinated BALB/c mice. The Thai A type B cell epitope

peptide bound with poly-lysine antigen (BLO antigen) showed increased IL-2 productivity of 5100 +/- 1000.
Dwg.0/2

L17 ANSWER 9 OF 9 WPIDS (C) 2003 THOMSON DERWENT
AN 1993-303140 [38] WPIDS
DNC C1993-134985
TI Compsn. contg. selectively de-glycosylated HIV-1 envelope protein - shows improved protective immune response.
DC B04 D16
IN ESSEX, M E; LEE, C; LEE, T; LEE, W
PA (HARD) HARVARD COLLEGE
CYC 19
PI **WO 9317705** A1 19930916 (199338)* EN 45p
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE
W: CA JP
EP 631506 A1 19950104 (199506) EN
R: DE FR GB IT
JP 07504569 W 19950525 (199529)
EP 631506 A4 19970730 (199813)
US 6103238 A 20000815 (200041)
ADT WO 9317705 A1 WO 1993-US1598 19930224; EP 631506 A1 EP 1993-906175 19930224, WO 1993-US1598 19930224; JP 07504569 W JP 1993-515726 19930224, WO 1993-US1598 19930224; EP 631506 A4 EP 1993-906175 19930224; US 6103238 A US 1992-850770 19920313
FDT EP 631506 A1 Based on WO 9317705; JP 07504569 W Based on WO 9317705
PRAI US 1992-850770 19920313

AB WO 9317705 A UPAB: 19931123
Compsn. comprises a mutant recombinant human immunodeficiency virus type 1 (HIV-1) envelope glycoprotein (I), which is mutated in its prim. aminoacid sequence w.r.t a wild type HIV-1 envelope glycoprotein, but is effective when present as a component of a complete HIV virion to enable viral infectivity. (I) includes at least one N-linked carbohydrate consensus aminoacid sequence mutation so as to effect partial deglycosylation, the mutation being positioned between the C terminus of gp. 120 and the Cys at the N-terminal side of the gp. 20 cysteine loop contg. the third hypervariable sequence (v3), the Cys being approximately at aminoacid position 296. (I) is sufficiently deglycosylated such that the total mol. mass of the mutant gp 120 component is less than 90% of the corresp. fully glycosylated wild type gp. 120 component.
ADVANTAGE - Glycosylation serves to reduce or prevent immunological recognition of envelope protein domains. Selective deglycosylation enables an immune response to these domains and improves the opportunity for a protective immune response. Thus (I) would be more effective in elicity a protective immune response in people.
Dwg.0/7

L19 ANSWER 6 OF 33 MEDLINE
93103816 Document Number: 93103816. PubMed ID: 1466960. Oral priming followed by parenteral immunization with HIV-immunosomes induce HIV-1-specific salivary and circulatory IgA in mice and rabbits. Thibodeau L; Tremblay C; Lachapelle L. (AIDS Laboratory, Institut Armand Frappier, University of Quebec, Laval, Canada.) AIDS RESEARCH AND HUMAN RETROVIRUSES, (1992 Aug) 8 (8) 1379. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

L23 ANSWER 10 OF 10 MEDLINE
93112220 Document Number: 93112220. PubMed ID: 1282012. Antibody-dependent cellular cytotoxicity (ADCC) is directed against immunodominant epitopes of the envelope proteins of human immunodeficiency virus 1 (HIV-1). Ziegner U H; Frank I; Bernatowicz A; Starr S E; Streckert H J. (Division of Infectious Diseases and Immunology, Children's Hospital of Philadelphia, Pennsylvania.) VIRAL IMMUNOLOGY, (1992 Winter) 5 (4) 273-81. Journal code: 8801552. ISSN: 0882-8245. Pub. country: United States. Language: English.

AB In this study, epitopes of HIV envelope proteins that are involved in ADCC were identified. Peripheral blood mononuclear cells (PBMC) were obtained from adults with asymptomatic HIV infection or early symptoms of AIDS. These PBMC, which were reported to be "armed" in vivo with HIV-specific antibodies, were used as effector cells in 51Cr release assays. Target cells consisted of CD4 lymphocytes from healthy seronegative donors, coated with the IIIB strain of HIV-1 or with one of seven synthetic peptides. Cytotoxicity was detected against CD4 lymphocytes coated with HIV-1 IIIB or with the peptides env aa 507-518, corresponding to the carboxy-terminus of gp120, and env aa 597-611, corresponding to the region of the cysteine loop of gp41. The magnitude of target cell lysis was directly related to the quantity of peptide used. In contrast, target cells coated with the peptide gag aa 129-135, corresponding to the p17/p24 cleavage region of the gag precursor, were not killed. The same immunodominant regions which were involved in ADCC were recognized in enzyme-linked immunoabsorbent assays (ELISA) by the majority of 107 sera from HIV-infected adults. We conclude that the immunodominant epitopes located at the carboxy-terminus of gp120 and the cysteine loop of gp41 serve as recognition structure for antibodies, capable of mediating ADCC against HIV-infected cells.

L23 ANSWER 1 OF 10 MEDLINE
2002150622 Document Number: 21880835. PubMed ID: 11883006. Characterization of neutralization epitopes of simian immunodeficiency virus (SIV) recognized by rhesus monoclonal antibodies derived from monkeys infected with an attenuated SIV strain. Cole K S; Alvarez M; Elliott D H; Lam H; Martin E; Chau T; Micken K; Rowles J L; Clements J E; Murphey-Corb M; Montelaro R C; Robinson J E. (Department of Molecular Genetics and Biochemistry, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania 15261, USA.) VIROLOGY, (2001 Nov 10) 290 (1) 59-73. Journal code: 0110674. ISSN: 0042-6822. Pub. country: United States. Language: English.

AB A major limitation in the simian immunodeficiency virus (SIV) system has been the lack of reagents with which to identify the antigenic determinants that are responsible for eliciting neutralizing antibody responses in macaques infected with attenuated SIV. Most of our information on SIV neutralization determinants has come from studies with murine monoclonal antibodies (MAbs) produced in response to purified or

recombinant SIV envelope proteins or intact SIV-infected cells for relatively short periods of time. While these studies provide some basic information on the potential immunogenic determinants of SIV envelope proteins, it is unclear whether these murine MAbs identify epitopes relevant to antibody responses elicited in monkeys during infection with either wild-type or attenuated SIV strains. To accomplish maximum biological relevance, we developed a reliable method for the production of rhesus monoclonal antibodies. In the present study, we report on the production and characterization of a unique panel of monoclonal antibodies derived from four individual monkeys inoculated with SIV/17E-CL as an attenuated virus strain at a time when protective immunity from pathogenic challenge was evident. Results from these studies identified at least nine binding domains on the surface envelope glycoprotein; these included linear determinants in the V1, V2, cysteine loop (analogous to the V3 loop in human immunodeficiency virus type 1), and C5 regions, as well as conformational epitopes represented by antibodies that bind the C-terminal half of gp120 and those sensitive to defined mutations in the V4 region. More importantly, three groups of antibodies that recognize closely related, conformational epitopes exhibited potent neutralizing activity against the vaccine strain. Identification of the epitopes recognized by these neutralizing antibodies will provide insight into the antigenic determinants responsible for eliciting neutralizing antibodies in vivo that can be used in the design of effective vaccine strategies.

L23 ANSWER 2 OF 10 MEDLINE
2000459016 Document Number: 20375034. PubMed ID: 10915074. Human immunodeficiency virus type 1 subtype E envelope recombinant peptides containing naturally immunogenic epitopes. Chang S Y; Vithayasai V; Vithayasai P; Essex M; Lee T H. (Department of Immunology and Infectious Diseases, Harvard School of Public Health, Boston, Massachusetts 02115, USA.) JOURNAL OF INFECTIOUS DISEASES, (2000 Aug) 182 (2) 442-50. Journal code: 0413675. ISSN: 0022-1899. Pub. country: United States. Language: English.

AB A series of recombinant peptides of the human immunodeficiency virus type 1 (HIV-1) subtype E envelope were used to address the question of whether immunogenic epitopes similar to those described for the subtype B envelope are also present in structurally analogous regions of another HIV-1 subtype with divergent sequences. Five recombinant peptides, covering the V2 and V3 domains of gp120, the cysteine-loop region of gp41, a gp41 region involved in oligomerization, and the cytoplasmic tail of gp41, were found to react with >50% of the serum samples analyzed. All but the V2 region in the HIV-1 subtype B envelope have been reported to contain continuous epitopes that are highly immunogenic during natural infection. This finding suggests that, despite the sequence divergence between subtype E and B envelopes, most of the continuous epitopes that are highly immunogenic during natural infection are located at structurally analogous regions of the envelope.

L23 ANSWER 3 OF 10 MEDLINE
2000171549 Document Number: 20171549. PubMed ID: 10706739. CCR5-reactive antibodies in seronegative partners of HIV-seropositive individuals down-modulate surface CCR5 in vivo and neutralize the infectivity of R5 strains of HIV-1 In vitro. Lopalco L; Barassi C; Pastori C; Longhi R; Burastero S E; Tambussi G; Mazzotta F; Lazzarin A; Clerici M; Siccardi A G. (Department of Biological and Technological Research and Infectious Diseases Clinic, San Raffaele Scientific Institute, Milano, Italy.. lopalco.lucia@hsr.it) . JOURNAL OF IMMUNOLOGY, (2000 Mar 15) 164 (6) 3426-33. Journal code: 2985117R. ISSN: 0022-1767.

Pub. country: United States. Language: English.

AB Exposure to HIV does not necessarily result in infection. Because primary HIV infection is associated with CCR5-tropic HIV variants (R5), CCR5-specific Abs in the sera of HIV -seronegative, HIV-exposed individuals (ESN) might be associated with protection against infection. We analyzed sera from ESN, their HIV-infected sexual partners (HIV+), and healthy controls (USN) searching for CCR5-specific Abs, studying whether incubation of PBMC with sera could prevent macrophage inflammatory protein 1 beta (Mip1 beta) (natural ligand of CCR5) binding to CCR5. Results showed that Mip1 beta binding to CCR5 was not modified by sera of either 40 HIV+ or 45 USN but was greatly reduced by sera of 6/48 ESN. Binding inhibition was due to Abs reactive with CCR5. The CCR5-specific Abs neutralized the infectivity of primary HIV isolates obtained from the corresponding HIV+ partners and of R5-primary HIV strains, but not that of CXCR4-tropic or amphitropic HIV strains. Immunoadsorption on CCR5-transfected, but not on CXCR4-transfected, cells removed CCR5-specific and virus-neutralizing Abs. Epitope mapping on purified CCR5-specific Abs showed that these Abs recognize a conformational epitope in the first cysteine loop of CCR5 (aa 89-102). Affinity-purified anti-CCR5-peptide neutralized the infectivity of R5 strains of HIV-1. Anti-CCR5 Abs inhibited Mip1beta-induced chemotaxis of PBMC from healthy donors. PBMC from two ESN (with anti-CCR5 Abs) were CCR5-negative and could not be stimulated by Mip1beta in chemotaxis assays. These results contribute to clarifying the phenomenon of immunologic resistance to HIV and may have implications for the development of a protective vaccine.

L23 ANSWER 4 OF 10 MEDLINE

2000122461 Document Number: 20122461. PubMed ID: 10655384. Analysis of genetic variability within the immunodominant epitopes of envelope gp41 from human immunodeficiency virus type 1 (HIV-1) group M and its impact on HIV-1 antibody detection. Dorn J; Masciotra S; Yang C; Downing R; Biryahwaho B; Mastro T D; Nkengasong J; Pieniazek D; Rayfield M A; Hu D J; Lal R B. (HIV Immunology and Diagnostics Branch, National Center for HIV, STD and TB Prevention, Centers for Disease Control and Prevntion, Atlanta, Georgia 30333, USA.) JOURNAL OF CLINICAL MICROBIOLOGY, (2000 Feb) 38 (2) 773-80. Journal code: 7505564. ISSN: 0095-1137. Pub. country: United States. Language: English.

AB The serodiagnosis of human immunodeficiency virus type 1 (HIV-1) infection primarily relies on the detection of antibodies, most of which are directed against the immunodominant regions (IDR) of HIV-1 structural proteins. Among these, the N-terminal region of gp41 contains cluster I (amino acids [aa] 580 to 623), comprising the cytotoxic T-lymphocyte epitope (AVERYLKDQQLL) and the cysteine loop (CSGKLIC), and cluster II (aa 646 to 682), comprising an ectodomain region (ELDKWA). To delineate the epitope diversity within clusters I and II and to determine whether the diversity affects serologic detection by U.S. Food and Drug Administration (FDA)-licensed enzyme immunoassay (EIA) kits, gp41 Env sequences from 247 seropositive persons infected with HIV-1 group M, subtypes A (n = 42), B (n = 62), B' (n = 13), C (n = 38), D (n = 41), E (n = 18), F (n = 27), and G (n = 6), and 6 HIV-1-infected but persistently seronegative (HIPS) persons were analyzed. While all IDR were highly conserved among both seropositive and HIPS persons, minor amino acid substitutions (<20% for any one residue, mostly conservative) were observed for all subtypes, except for B', in comparison with the consensus sequence for each subtype. Most importantly, none of the

observed substitutions among the group M plasma specimens affected antibody detection, since all specimens (n = 152) tested positive with all five FDA-licensed EIA kits. Furthermore, all specimens reacted with a group M consensus gp41 peptide (WGIKQLQARVLAVERYLKDQQLLGIWGCSGKLICTTAVPWNA SW), and high degrees of cross-reactivity (>80%) were observed with an HIV-1 group N peptide, an HIV-1 group O peptide, and a peptide derived from the homologous region of gp41 from simian immunodeficiency virus from chimpanzee (SIVcpz). Taken together, these data indicate that the minor substitutions observed within the IDR of gp41 of HIV-1 group M subtypes do not affect antibody recognition and that all HIV-1-seropositive specimens containing the observed substitutions react with the FDA-licensed EIA kits regardless of viral genotype and geographic origin.

L23 ANSWER 5 OF 10 MEDLINE
97418745 Document Number: 97418745. PubMed ID: 9274821. Diversity of the immunodominant epitope of gp41 of HIV-1 subtype O and its validity for antibody detection. Eberle J; Loussert-Ajaka I; Brust S; Zekeng L; Hauser P H; Kaptue L; Knapp S; Damond F; Saragosti S; Simon F; Gurtler L G. (Pettenkofer Institute, University of Munchen, Germany.) JOURNAL OF VIROLOGICAL METHODS, (1997 Aug) 67 (1) 85-91. Journal code: 8005839. ISSN: 0166-0934. Pub. country: Netherlands. Language: English.

AB The immunodominant regions of the gp41 from 13 HIV-1 subtype O strains from Cameroon, 11 from France and one from Germany were sequenced. The amino acid sequences were compared to those of the 3 published HIV-1 subtype O isolates, ANT70, MVP-5180 and VAU. All HIV-1 subtype O isolates had a very conserved amino acid sequence in this region and showed a subtype O specific structure. Within the cysteine loop there was a positive charge of two basic amino acids, arginine and lysine. Only two strains (CM.6778 and CM.8161) showed an acidic amino acid in this loop. None of the isolates showed the same amino acid sequence in this immunodominant region. A 25 residue peptide from the immunodominant domain of gp41 of the MVP-5180 strain was synthesized, cycled to form the cysteine-loop and coated to microtiter plates. Antibody binding was detected by indirect ELISA using an enzyme labeled anti-human IgG. Out of 111 anti-HIV -1 positive specimens, collected mainly from Cameroonian HIV infected patients, only 10 were not reactive in this assay. The 42 anti-HIV-1 subtype O positive specimens gave all a reaction above cut off. Despite the diversity found in the amino acid sequences within the 25 isolates a peptide-based indirect ELISA representing the immunodominant epitope of the strain MVP-5180 successfully detected all the anti-HIV-O sera so far tested, pointing to the importance of adding such a peptide for correct identification of HIV-1 subtype O infected patients, while some assays without HIV-O specific antigens partially fail to detect all anti-HIV-O specimens.

L23 ANSWER 6 OF 10 MEDLINE
96099479 Document Number: 96099479. PubMed ID: 8523579. Single amino acid substitution in constant region 1 or 4 of gp120 causes the phenotype of a human immunodeficiency virus type 1 variant with mutations in hypervariable regions 1 and 2 to revert. Wang W K; Essex M; Lee T H. (Department of Cancer Biology, Harvard School of Public Health, Boston, Massachusetts 02115, USA.) JOURNAL OF VIROLOGY, (1996 Jan) 70 (1) 607-11. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB The second major cysteine loop of human immunodeficiency virus type 1 envelope glycoprotein gp120 contains 5 to 11 consensus N-linked glycosylation sites, which is

disproportionately higher than the number of such sites found in other regions of gp120. Amino acid substitutions introduced at three of six N-linked glycosylation sites in this region of an infectious molecular clone, HXB2, resulted in severe impairment of virus infectivity. Isolation and genetic characterization of a revertant of this mutant revealed an isoleucine-for-valine substitution at position 84 in constant region 1 and an isoleucine-for-methionine substitution at position 434 in constant region 4. Further mutational analysis indicated that either isoleucine substitution was sufficient to confer the revertant phenotype. These findings demonstrate that V1/V2 not only functionally interacts with C4, as previously reported, but also interacts with C1. The observation that compensatory changes do not involve regeneration of N-linked glycosylation sites in the second major cysteine loop suggests that replication of human immunodeficiency virus type 1 in vitro is independent of the presence of a disproportionate number of N-linked glycosylation sites within this loop.

L23 ANSWER 7 OF 10 MEDLINE

94365973 Document Number: 94365973. PubMed ID: 7521921. A simian immunodeficiency virus envelope V3 cytotoxic T-lymphocyte epitope in rhesus monkeys and its restricting major histocompatibility complex class I molecule Mamu-A*02. Watanabe N; McAdam S N; Boyson J E; Piekarczyk M S; Yasutomi Y; Watkins D I; Letvin N L. (Harvard Medical School, Beth Israel Hospital, Boston, Massachusetts 02215.) JOURNAL OF VIROLOGY, (1994 Oct) 68 (10) 6690-6. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB The use of the simian immunodeficiency virus (SIV) macaque model for assessing human immunodeficiency virus vaccine strategies will be facilitated by the characterization of predominant SIV cytotoxic T-lymphocyte (CTL) epitopes and their restricting major histocompatibility complex (MHC) class I molecules in macaque species. We now define a rhesus monkey SIVmac CTL epitope in the third hypervariable region of the envelope glycoprotein of the virus. This epitope, YNLTMKCR, contains the first two amino acids of a cysteine-cysteine loop which is the SIVmac analog of the human immunodeficiency virus type 1 V3 loop. We also employed one-dimensional isoelectric focusing to characterize the MHC class I molecule of the rhesus monkey that binds this SIVmac envelope peptide fragment. Cloning and sequencing the cDNA encoding this rhesus monkey MHC class I molecule demonstrates that it is a newly described HLA-A homolog, Mamu-A*02. This viral CTL epitope and its restricting MHC class I molecule will facilitate the use of the SIVmac rhesus monkey model for studies of envelope-based vaccine strategies and for exploring AIDS immunopathogenesis.

L23 ANSWER 8 OF 10 MEDLINE

94202300 Document Number: 94202300. PubMed ID: 8151778. Extensive envelope heterogeneity of simian immunodeficiency virus in tissues from infected macaques. Campbell B J; Hirsch V M. (Immunodeficiency Viruses Section, National Institute of Allergy and Infectious Diseases, Rockville, Maryland 20852.) JOURNAL OF VIROLOGY, (1994 May) 68 (5) 3129-37. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB The extent of virus genetic variation within tissues and peripheral blood mononuclear cells (PBMC) from two simian immunodeficiency virus (SIV)-infected macaques was analyzed. The products of PCR amplification of two regions, region 1 (SIV V1 region) and region 2 (region corresponding to the human immunodeficiency

virus V3 cysteine loop and part of the C3 region immediately downstream), of the SIV envelope were examined for single-stranded conformation polymorphism followed by sequence analysis of selected clones. The V1 region of the SIV envelope of viruses present within lymphoid tissues displayed extensive heterogeneity, while viral populations within the PBMC and brain appeared to be less variable. Region 2 heterogeneity in both animals was generally confined to three residues in a tissue-specific manner. In addition, virus from the brains of both animals appeared to be distinct compared with viruses present in other tissues and PBMC of the same animal, both in the pattern of PCR-single-stranded conformation polymorphism SCP and in the sequence of region 2. These studies revealed that the tissues of SIV-infected macaques were a reservoir for viral variants distinct from those seen in PBMC.

L23 ANSWER 9 OF 10 MEDLINE
93152284 Document Number: 93152284. PubMed ID: 7678970. Identification of human immunodeficiency virus type 1 glycoprotein gp120/gp41 interacting sites by the idiotypic mimicry of two monoclonal antibodies. Lopalco L; Longhi R; Ciccomascolo F; De Rossi A; Pelagi M; Andronico F; Moore J P; Schulz T; Beretta A; Siccardi A G. (Centro San Luigi H.S.R. Milano, Italy.) AIDS RESEARCH AND HUMAN RETROVIRUSES, (1993 Jan) 9 (1) 33-9. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB A sequence of four amino acid residues amino-terminal to the only intramolecular disulphide bond of the human immunodeficiency virus type 1 (HIV-1) transmembrane protein gp41 is recognized by an anti-idiotypic antibody (9G5A) raised against another monoclonal antibody (M38), which recognizes the C5 region of gp120. 9G5A is an Ab2 beta antibody (internal image of the M38 epitope) in that it inhibits the interaction of M38 to its antigen. The binding of 9G5A to gp41 can be inhibited by M38 showing that the two antibodies interact via their paratopes. 9G5A neutralizes HIV-1 infection and syncytia formation. Ab3 antibodies induced in mice and rabbits immunized with 9G5A also can neutralize virus in both assays. These data show that the M38-defined epitope of the carboxy-terminal region of gp120 interacts with the 9G5A-defined epitope of gp41, and that this interaction can be reproduced by the idiotypic mimicry of the two antibodies. The results are consistent with a proposed molecular model of the two env regions which predicts the presence, within the C5 region of gp120, of a large intramolecular pocket that is contacted by the gp41 cysteine loop.

L23 ANSWER 10 OF 10 MEDLINE
93112220 Document Number: 93112220. PubMed ID: 1282012. Antibody-dependent cellular cytotoxicity (ADCC) is directed against immunodominant epitopes of the envelope proteins of human immunodeficiency virus 1 (HIV-1). Ziegner U H; Frank I; Bernatowicz A; Starr S E; Streckert H J. (Division of Infectious Diseases and Immunology, Children's Hospital of Philadelphia, Pennsylvania.) VIRAL IMMUNOLOGY, (1992 Winter) 5 (4) 273-81. Journal code: 8801552. ISSN: 0882-8245. Pub. country: United States. Language: English.

AB In this study, epitopes of HIV envelope proteins that are involved in ADCC were identified. Peripheral blood mononuclear cells (PBMC) were obtained from adults with asymptomatic HIV infection or early symptoms of AIDS. These PBMC, which were reported to be "armed" in vivo with HIV-specific antibodies, were used as effector cells in 51Cr release assays. Target cells consisted of CD4 lymphocytes

from healthy seronegative donors, coated with the IIIB strain of HIV-1 or with one of seven synthetic peptides. Cytotoxicity was detected against CD4 lymphocytes coated with HIV-1 IIIB or with the peptides env aa 507-518, corresponding to the carboxy-terminus of gp120, and env aa 597-611, corresponding to the region of the cysteine loop of gp41. The magnitude of target cell lysis was directly related to the quantity of peptide used. In contrast, target cells coated with the peptide gag aa 129-135, corresponding to the p17/p24 cleavage region of the gag precursor, were not killed. The same immunodominant regions which were involved in ADCC were recognized in enzyme-linked immunoabsorbent assays (ELISA) by the majority of 107 sera from HIV-infected adults. We conclude that the immunodominant epitopes located at the carboxy-terminus of gp120 and the cysteine loop of gp41 serve as recognition structure for antibodies, capable of mediating ADCC against HIV-infected cells.

L26 ANSWER 6 OF 11 MEDLINE
96171638 Document Number: 96171638. PubMed ID: 8574151. Distribution of linear antigenic epitopes on GP120 encoded in sibling clones of novel New York HIV-1 subtype B isolates. Riley J P; Pestano G A; Harewood K; Alfred L J; Guyden J; Boto W M. (Department of Biology and Chemistry, City College of the City University of New York, NY 10031, USA.) CELLULAR AND MOLECULAR BIOLOGY, (1995) 41 Suppl 1 S83-91. Journal code: 9216789. ISSN: 0145-5680. Pub. country: France. Language: English.

AB We have initiated studies to characterize the predominant subtypes of HIV-1 which account for infections in a defined cohort of intravenous (IV) drug addicts. A region of ENV encoding the C2 to the V5 regions was amplified from the leukocytes of two subjects currently enrolled in a methadone maintenance program at the Addiction Research and Treatment Corporation (ARTC), in Brooklyn, New York. This region of the viral genome encodes the principal neutralizing determinant (PND) located in the V3 loop, the immunogenic CD4-binding site, and six other linear antigenic epitopes in the envelope glycoprotein, gp120. Phylogenetic tree analysis of the nucleotide sequences showed that the sibling clones RT1.4, RT1.15, RT1.17, RT1.21 and RT3.6, RT3.10, RT3.11, RT3.12 and RT3.15 derived from the isolates, RT1 and RT3, respectively, cluster with "group B" viruses at 99% confidence level. Marked intra-patient and inter-patient sequence variation was apparent in the V3 loop. The divergence included the presence of a previously unreported hexapeptide GPWGTF at the cap of the loop in the clones from RT1. The North American consensus hexapeptide, GPGRAF , was identified in the cap of the loop from the clones of RT3. Four of the five sibling clones from RT3 were closely related whereas the other clone, RT3.15, displayed five amino acid mutations downstream of the V3 cap. To assess the effect of sequence variation on the distribution of linear antigenic epitopes, complementary computer software programs, were used to analyze the gp120 residues. Eight analogous antigenic epitopes were identified in the clones from both isolates despite the marked divergence in the primary sequences.(ABSTRACT TRUNCATED AT 250 WORDS)

L28 ANSWER 19 OF 21 MEDLINE
95138191 Document Number: 95138191. PubMed ID: 7836454. Local and global structural properties of the HIV-MN V3 loop.
Catasti P; Fontenot J D; Bradbury E M; Gupta G. (Theoretical Biology and Biophysics Group, Los Alamos National Laboratory, New Mexico 87545.) JOURNAL OF BIOLOGICAL CHEMISTRY, (1995 Feb 3) 270 (5) 2224-32. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB Studies of the feasibility of a subunit vaccine to protect against human immunodeficiency virus (HIV) infection have principally focused on the third variable (V3) loop. The principal neutralizing determinant (PND) of HIV -1 is located inside the V3 loop of the surface envelope glycoprotein, gp120. However, progress toward a PND-based vaccine has been impeded by the amino acid sequence variability in the V3 loops of different HIV isolates. Theoretical studies revealed that the variability in sequence and structure of the V3 loop is confined to the N- and C-terminal sides of the conserved GPG crest. This leaves three regions of the V3 loop conserved both in sequence and secondary structure. We present the results of NMR studies that test the validity of our theoretical predictions. Structural studies are reported for the HIV-V3 loop (HIV-MN) in the linear and cyclic (S-S-bridged) forms. For the V3 loop sequence of the HIV-MN isolate, the three conserved secondary structural elements are as underlined below: turns turn helix CTRPNYNKRKRIHIGPGRAFYTTKNIIGTIRO AHC Finally, the conformational requirement of the PND in the V3 loop-antibody interaction is tested by monitoring the monoclonal antibody binding to the HIV-MN V3 loop in the linear and cyclic forms by enzyme-linked immunosorbent assay. The binding data reveal that the cyclic V3 loop is a better ligand for the monoclonal antibodies than the linear form although the latter has the same sequence. This means that the monoclonal antibodies recognize the PNDs as conformational epitopes.